



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**IND:** SN-073

**Drug:** Adefovir Dipivoxil for the Treatment of Hepatitis B Infection

**Date:** August 11, 1999

**To:** Bridget P. Binko, Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager,  
HFD-530

**Through:** Greg Soon, PhD, Statistical Reviewer

**Concur:** Girish Aras, PhD, Statistical Review Team Leader  
Jeffrey Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Statistical Reviewer's Comments

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Please refer to your IND application for adefovir dipivoxil for the treatment of patients with chronic hepatitis B virus infection and to Protocol GS-98-437, entitled *A Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with HBeAg Chronic Hepatitis B Virus Infection*, (IND SN-047 dated November 24, 1998.)

1. For the histology, please use the proportion of subjects who have "improvement" in the necroinflammatory score and no worsening in the fibrosis score as the primary endpoint. See Medical Officer's comment #2 (Division Facsimile Memorandum dated July 27, 1999) for further details.
2. Please provide the following exploratory analyses for histology:
  - Define a new score as follows: New score = sum of necroinflammatory scores, if fibrosis score is not worsened. New score = 18, if fibrosis score has worsened when compared to the baseline.

The score of 18 is the worst possible for necroinflammatory change. Worsening of fibrosis is considered worse than any deterioration of necroinflammatory score here.

Please compare the new scores using Mann-Whitney test and construct 95% confidence intervals of the differences between treatment groups.

- Compare the sums of four-component histologic improvement using Mann-Whitney test and construct 95% confidence intervals of the differences between treatment groups.
  - Compare the sums of necroinflammatory components of histologic improvement using Mann-Whitney test and construct 95% confidence intervals of the differences between treatment groups.
  - For each component of the histology, compare the improvements using Mann-Whitney test and construct 95% confidence intervals of the differences between treatment groups.
3. Please clarify if all the dosage forms (30mg, 10mg, 5mg, and placebo) used in this study are identical.
  4. For HBV DNA analysis, please:
    - Plot the median change from baseline for HBV DNA over time.
    - Provide analysis of HBV DNA proportions below LOQ over time.
  5. For "the time to first HBeAg seroconversion", we recommend that subjects lost to follow-up and withdrawals due to AEs be regarded as censored at the end of the study.
  6. For "the time to failure of ALT normalization", please specify how subjects lost to follow-up and withdrawals due to AEs will be coded in the analysis.

Suggestions:

- Withdrawal due to AEs = failure at time of AE.
- Lost to follow-up = failure at time of lost to follow-up (intent to treat)
- Lost to follow-up = censored at time of lost to follow-up (as treated).

Please make a choice and explain.

7. Please clarify if interim analyses may result in stopping of the trial. If so, please describe the rules for stopping the trial and the statistical adjustment needed for statistical tests.

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## FACSIMILE MEMORANDUM

**DATE:** July 27, 1999

**TO:** Alan S. Taylor, PhD, Vice President, Drug Assessment

**SPONSOR:** Gilead Sciences, Inc

**FROM:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, HFD-530

**THROUGH:** Tan Nguyen, MD, PhD, Regulatory Review Officer  
Theresa Wu, MD, MPH, Medical Review Team Leader (Acting)

**SUBJECT:** Comments on \_\_\_\_\_ /SN-073

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Please refer to your IND application for adefovir dipivoxil for the treatment of patients with chronic hepatitis B virus infection and to Protocol GS-98-437, entitled *A Double-Blind, Randomized, Placebo-Controlled Study of Adefovir Dipivoxil for the Treatment of Patients with HBeAg Chronic Hepatitis B Virus Infection* (\_\_\_\_\_) /SN-047 dated November 24, 1998.)

Please note that comments from the Statistical Reviewer will follow shortly.

1. Although the nephrotoxicity data from Study GS-98-412 raise a safety concern for prolonged use of adefovir 30 mg/day dose, the Division concurs that treatment group 3 (adefovir 30 mg/day for six months) should still be included in this study. In this setting, the interpretation of liver biopsy data at the end of month 12 would be difficult as you indicated. However, useful information may be gained by exploring the efficacy of different treatment strategies (*i.e.*, group 1 versus group 3) based on histologic improvement and HBeAg/anti-HBe seroconversion rate at the end of the first year.
2. The Division stands by its previous recommendation that the primary histologic endpoint includes assessments of both necroinflammatory activity and fibrosis. Multiple statistical tests for significance can be avoided by defining histologic improvement as improvement of necroinflammatory score in the presence of improved or unchanged fibrosis score. If a reduction of at least two points in the Knodell score is to be used as an indication of necroinflammatory improvement, please provide clinicopathologic evidence to support this cut-off value.
3. The analysis of HBeAg/anti-HBe seroconversion rate may be complicated by the fact that low-level HBeAg production may continue post-seroconversion and be masked by excess anti-HBe antibodies. Please clarify how to overcome this problem.

4. Please provide evidence to support the clinical significance of DAVG<sub>12</sub> of ~~HBV~~ DNA, i.e., its correlation with disease activity and/or progression.
5. It is recommend that adefovir treatment be permanently discontinued in patients with persistently elevated ALT/AST levels who exhibit worsening clinical picture (*e.g.*, nausea, vomiting, abdominal pain, fever, etc.), and/or concomitantly elevated bilirubin, prolonged prothrombin time, decreased albumin, or significant rise in HBV DNA titer.
6. We acknowledge your revised hepatotoxicity management scheme. However, for this study, it is still recommended that temporary interruption of adefovir treatment be considered in patients with asymptomatic, persistent ALT/AST elevations to above ten times the upper limit of normal. For patients with high ALT/AST baseline levels (*e.g.*, grade 2 WHO Toxicity Grading Scale or higher), we recommend that treatment be interrupted if ALT/AST elevations are persistently greater than two to three times the baseline levels. However, if treatment interruption (or dose reduction) is not considered, these patients should be monitored at close intervals (*e.g.*, weekly or more frequently as clinically indicated) with clinical examination and laboratory tests.
7. While the clinical judgement of the investigators to determine if an adverse event is related to treatment is valuable, we recommend that the protocol include criteria for uniformed assessment of this relationship.
8. It is recommend that the information on nephrotoxicity associated with adefovir treatment in patients with chronic hepatitis B be included in the Investigator's Brochure. The investigators participating in ongoing "compassionate" treatment protocols should be formally notified.
9. We recommend that the informed consent form for all ongoing treatment protocols with adefovir be revised to reflect the above nephrotoxicity findings. All patients who have enrolled in these protocols should be re-consented.
10. Adefovir treatment should be discontinued if a patient tests positive for HIV at any time during the study.
11. Please clarify whether a follow-on program to monitor patients for long-term safety, treatment effects, and emergence of viral resistance will be implemented as a separate protocol.
12. Please review section 1.5 of the protocol for the following discrepancies:
  - A. The protocol states "... no patient had a creatinine value that had risen by  $\geq 0.5$  mg/dL above the baseline value" (page 16). The submitted data shows that patients #13 and #89 had creatinine elevations of 0.5 mg/dL and 0.6 mg/dL, respectively, after week 32 of treatment.
  - B. The protocol states "...in 6 of these 8 patients [with creatinine elevation of 0.3 to 0.4 mg/dL] there are associated abnormalities on urinalysis." The submitted data show that all nine patients with elevated creatinine levels had positive glycosuria and/or proteinuria.

- C. The protocol states "...in 3 of the 16 patients (19%), phosphate levels were below 2.0 mg/dL." The submitted data show there were six patients with phosphorus levels falling below 2.0 mg/dL, four of whom had concomitant elevation of creatinine to greater than 0.3 mg/dL above baseline.

Please note that we received your facsimile of today and it was given to Dr. Nguyen for review. **However, Protocol GS-98-437 may proceed only in the manner suggested in this facsimile memorandum for SN-073.**

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville, MD 20857

## FACSIMILE MEMORANDUM

IND/NDA                      — SN-073

DRUG:                      Adefovir Dipivoxil to treat Hepatitis B infection

DATE:                      July 08, 1999

TO:                        Ellen Wallace, Regulatory Affairs

SPONSOR:                Gilead Sciences, Inc

FROM:                    Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager

THROUGH:               Tan Nguyen, MD, PhD, Regulatory Review Officer

CONCUR:                Jeffrey Murray, MD, MPH, Medical Review Team Leader

SUBJECT:                Comments and Request for Information

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We have received a desk copy of — Adefovir Dipivoxil, SN-073 and the corrected replacement page 126.

The substantial changes in SN-073 require reviews by various disciplines. In order to expedite our review, we request that you send a copy of Protocol GS-98-437 **immediately prior to** the changes contained in SN-073. We will endeavor to complete our review as quickly as possible.

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## FACSIMILE MEMORANDUM

**DATE:** July 7, 1999

**TO:** Alan S. Taylor, PhD, Vice President, Drug Assessment

**SPONSOR:** Gilead Sciences, Inc

**FROM:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager

**THROUGH:** Lauren Iacono-Connors, PhD, Microbiology Team Leader  
Jeffrey Murray, MD, MPH, Medical Review Team Leader

**SUBJECT:** Comments on , serial 061

These comments are being conveyed on behalf of Dr. Lauren Iacono-Connors, Microbiology Team Leader, and are directed toward serial 61.

1. The kit package insert is useful for describing how the HBV Amplicor Monitor assay works and the precise methodology. It does not however, give any information regarding quality control and quality assurance for the manufacturing of this kit. Until this kit is approved by the FDA it should be assumed that manufacturing is not controlled. To minimize potential assay performance variability, please consider use of kits from the same manufacturing lot numbers where possible.
2. In the HBV DNA assay performance characteristics data presented in this submission, both serum and plasma source material were used. Please note that no data were provided that shows equality in measurement results between serum and plasma specimens. Therefore, the HBV Amplicor Monitor™ assay performance characteristics data should be generated using the same source material as that proposed for the clinical trial, plasma.
3. The data provided in the "clinical sensitivity" section of the assay performance studies are not considered representative of the clinical sensitivity of the assay. The estimate of the HBV concentration within the specimen was generated using the same assay being tested. The division recommended in an earlier correspondence that the clinical specimens assessed in this type of study be quantified using independent and adequate methodology. In addition, it appears that only one clinical specimen was evaluated. As previously recommended, 200 unique clinical specimens be evaluated in order to establish 'clinical sensitivity.'
4. In the analysis of the effects of certain interfering substances on the HBV DNA assay the sponsor did not conduct the analysis using the low HBV DNA concentration. It is, therefore, not clear if the assay can perform as expected in the presence of these interfering substances at the assay's proposed limit of quantification. Please consider conducting additional studies to address the effects of interfering substances on the HBV DNA assay performance on a HBV specimen that is representative of the assay's proposed limit of quantification (1000 copies per mL).

5. The analysis of the effects of storage conditions and repeated freeze-thaw cycles of HBV specimens on the assay's performance did not include a low copy number HBV specimen. Since the assay is purported to be able to reproducibly detect HBV DNA at 1000 copies per mL, please consider conducting this assessment using the lowest concentration of HBV DNA expected to be reproducibly measured.

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Marsha Holloman, BS Pharm, JD  
Regulatory Project Manager  
Division of Antiviral Drug Products





**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service  
Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**FACSIMILE MEMORANDUM**

**DATE:** June 21, 1999

**TO:** Alan S. Taylor, PhD, Vice President, Drug Assessment

**SPONSOR:** Gilead Sciences, Inc

**FROM:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager

**THROUGH:** Tan Nguyen, MD, PhD, Regulatory Review Officer

**CONCUR:** Jeffrey Murray, MD, MPH, Medical Review Team Leader

**SUBJECT:** Comments on \_\_\_\_\_ SN-071

We acknowledge your proposed revision for reporting adverse events in HIV studies to investigators conducting chronic hepatitis B studies under \_\_\_\_\_, SN-071 as outlined in part 2 of the General Correspondence (*Summaries of Safety Information to be Provided on Biannual Basis.*) We concur with the plan as proposed.

**APPEARS THIS WAY  
ON ORIGINAL**

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## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** October 14, 1998

**TO:** Ellen Wallace, Ph.D., Regulatory Affairs

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Jeff Murray, M.D., M.P.H., Team Leader

**IND:** — Serial No. 041

**SUBJECT:** Clinical Comments for Protocol GS-98-435 entitled, "A randomized, open-label compassionate use study of adefovir dipivoxil at two doses for the treatment of YMDD mutant hepatitis B virus (HBV) infection in liver transplant recipients."

### Clinical Comments:

1. This small, uncontrolled, dose-ranging study may be useful to explore the activity of adefovir in HBV infected liver transplant patients but is unlikely to serve as a basis for a future regulatory filing.
2. It is recommended that the proportion of patients with HBV DNA suppression below the limit of quantification be considered in the primary efficacy analysis.
3. It is recommended that a baseline liver biopsy be obtained.
4. With regard to treatment-emergent hepatotoxicity, it is recommended that adefovir be withheld if ALT/AST levels are elevated to above 10X the upper limit of normal in patients with baseline ALT/AST levels lower than grade 3 (WHO Toxicity Grading Scale). For those patients with high ALT/AST baseline levels (grade 3/4) on entry, it is recommended that treatment be withheld if ALT/AST elevations are above 2X the baseline levels. This coincides with the management scheme discussed at the phase 2 assessment meeting on Oct. 9, 1998. It is also recommended that liver biopsy be strongly considered to differentiate between possible causes of hepatotoxicity (e.g., drug-induced toxicity, rejection, infections, or other causes) prior to resumption of treatment in these cases.

5. Patients in this study are likely to be exposed to multiple nephrotoxic agents (e.g., immunosuppressant agents, antibiotics, nonsteroidal anti-inflammatory drugs, etc.). Additionally, a number of these patients may also have had preexisting renal dysfunction. Therefore, it is recommended that interruption of adefovir be considered, at the investigator's discretion, for serum creatinine increases greater than 0.5 mg/dL above baseline. Assessment of creatinine clearance should be considered prior to resumption of treatment. It is also recommended that the protocol specify a list of potentially nephrotoxic drugs that should be avoided (if possible) during the study.
6. For grade 3 toxicities other than hepatic, renal, and CPK abnormalities, it is recommended that adefovir treatment be withheld until toxicities return to below grade 2 or baseline levels. It is also recommended that permanent discontinuation of study drug be considered if toxicities recur more than two times.
7. Please provide a rationale for the provision to allow adefovir dose escalation before week 16. Please clarify how patients with early dose escalation (prior to week 16) will be treated in final data analysis.
8. Since hepatitis B immunoglobulin (HBIG) is allowed in this trial, please clarify how the effects of HBIG will be accounted for in final data analysis.
9. Please provide a rationale for including patients with hepatitis D co-infection. Please clarify how the confounding effect of hepatitis D infection will be evaluated in the final data analysis.
10. Please address the plan for patients who may develop HBeAg seroconversion (loss of HBeAg and acquisition of HBeAb), i.e., whether they will continue to receive adefovir treatment, or whether treatment will be discontinued.
11. Please clarify how "active liver disease due to other causes" (section 3.2.1, protocol page 15) will be determined.
12. It is recommended that criteria for "lack of evidence of anti-HBV effect" (section 4.1.1, protocol page 17) be clearly defined in the protocol.
13. Please provide a sample informed consent form for our review.

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Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** October 5, 1998

**TO:** Ellen Wallace, Ph.D., Regulatory Affairs

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Jeff Murray, M.D., M.P.H., Team Leader

**IND:** ~~Serial No. 041 and 046~~

**SUBJECT:** Request for End of Phase 2 Meeting

Please refer to your submission dated August 25, 1998, in which you formally requested an "End-of- Phase 2" meeting for adefovir dipivoxil for the treatment chronic hepatitis B virus infection, this meeting has been scheduled for October 9, 1998. Also please refer to your submissions dated August 25, 1998 and October 1, 1998, which included background material for the October 9, 1998 meeting.

Based on review of the background documents, we intend to refer to this as a phase 2 assessment meeting for administrative and regulatory purposes. This reclassification will not affect the proposed agenda for the meeting, but will be noted in the official record.

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/S/

Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products

cc:

Original IND

Division File

HFD-530/MO TL/J.Murray

HFD-530/MO/T.Nguyen

HFD-530/RMO/D.Gump



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** August 21, 1998

**TO:** Gene Mason, Pharm.D., Directory, Regulatory Affairs

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Sam Maldonado, M.D., M.P.H., Acting Team Leader

**IND:** — Serial No. 040

**SUBJECT:** Comments on "Response to FDA Request for Information" for Study GS-96-412, Amendment # 4: *A Phase II Sequential Cohort, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Trial to Assess the Safety, Tolerability and Antiviral Activity of 3 Dose Levels of Oral Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection in Subjects with Elevated Transaminases.*

### Clinical Comments:

1. There is no compelling evidence to conclude whether hepatitis "flares" (WHO grade 3 or 4 ALT/AST elevations) are clearly unrelated to or induced by adefovir therapy. It is plausible that these abnormalities represent spontaneous exacerbations of disease activity in chronic hepatitis B infection.
2. There is no evidence to support the conclusion that the hepatitis "flares" reflect positive treatment response with adefovir with respect to viral suppression, serological conversions of HBV markers, or histological improvement.
3. There is no evidence to definitively rule out the possibility that these hepatitis "flares" would not result in catastrophic hepatic decompensation in patients with moderate or advanced liver disease.

4. It is difficult, if not impossible, to differentiate spontaneous hepatitis “flares” from hepatotoxicity effects of study drug based on laboratory evaluations. Therefore, continuation of study drug in the presence of potentially life-threatening (grade 4) ALT/AST elevations may pose a potentially serious threat to patient safety.
5. The cited AASLD abstract results are based on a very limited number of patients, some of whom also had HIV coinfection. They do not appear to provide convincing evidence to support the conclusion that ALT “flares” observed during adefovir treatment are secondary to beneficial activation of the immune response to HBV.

While we acknowledge your valid concern regarding the emergence of resistance mutants, based on the above observations we do not concur with your proposal to revise the criteria for grade 4 aminotransferase toxicities to “> 20x ULN and > 2x baseline level” and to use this revised grading as a basis for study drug discontinuation. These criteria, if followed, may potentially expose patients to unreasonable and significant risks of serious hepatic injury. In addition, there is no compelling evidence of any clinical benefit to justify these risks.

Additionally, we would like to have clarification on the following points:

1. Please clarify how hepatitis “flares” can be attributed to adefovir effects when similar “flares” have also been observed in patients on the control arm.
2. Please provide references to support the classification of mild, moderate and severe “flares.”
3. Please provide an update on the status of adefovir resistance monitoring.
4. Under section “5.2.3 Ongoing Studies” of the Investigator’s Brochure, the statement “There was no evidence of steatosis or microvesicular fat, mitochondrial damage or other evidence of drug toxicity,” which refers to the liver biopsy results of two patients in Study GS-96-412, appears inconsistent with the histopathological results on these liver biopsies. According to the pathology reports, both biopsies showed evidence of eosinophilic infiltrates “possibly representing drug reaction.” In addition, one biopsy (SP) had “diffuse hepatocellular swelling and the presence of rare single cell necrosis.” It is noted that there is no evidence to conclude that these findings are, indeed, unrelated to adefovir therapy.

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**/S/**

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Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



cc:

Original IND

Division File

HFD-530/MO ATL/S.Maldonado

HFD-530/MO/T.Nguyen

HFD-530/RMO/D.Gump



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** June 26, 1998

**TO:** Gene Mason, Pharm.D., Directory, Regulatory Affairs

**FROM:** Tan Nguyen., Medical Officer

**THROUGH:** Sam Maldonado, M.D., M.P.H., Acting Team Leader

**IND:** — Serial No. 039

**SUBJECT:** Comments on Study GS-96-412, Amendment # 4: *A Phase II Sequential Cohort, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Trial to Assess the Safety, Tolerability and Antiviral Activity of 3 Dose Levels of Oral Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection in Subjects with Elevated Transaminases.*

### Clinical Comments:

1. The current criteria for grade 4 aminotransferase (ALT, AST) toxicities, i.e., > 20x ULN and > 2x baseline value, may pose significant safety risks for study patients. We recommend that criteria for grade 4 aminotransferase toxicity be revised to > 10x UNL and > 2x baseline level.
2. According to the protocol, a dose of 125 mg/day of L-carnitine supplement is estimated to maintain carnitine levels within the normal range in patients receiving 30 mg/day adefovir (page 90, section 5.0). Since patients enrolled in the treatment extension will not receive carnitine supplement, we recommend that serum carnitine levels in these patients be monitored at closer intervals than proposed, at least initially (e.g., every two weeks for the first month, monthly for 2 months, and every two months subsequently).
3. Please clarify whether L-carnitine supplement will be given to patients in the treatment extension period when their levels fall below the upper limit of the normal range or the lower limit of the normal range (page 21).

4. We recommend that patients be informed about the potential risks associated with taking commercially available supplement containing D,L-carnitine in the Patient Informed Consent form.
5. We recommend that the Patient Informed Consent address the renal toxicity associated with adefovir administration.
6. We recommend that the statement "Liver inflammation has been seen with favorable response to treatment of chronic hepatitis B with other drugs, such as interferon and an experimental drug called lamivudine" (page 67, section "Risks of the Study") be deleted from the Patient Informed Consent due to its speculative nature.
7. We recommend that the statement "You will be closely monitored with physical examinations and blood tests to assess whether any inflammation you may developed is related to drug toxicity or a favorable response to treatment" (page 67, section "Risks of the Study") be revised to delete the reference to "favorable response to treatment" (please see related comment # 6).

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/s/

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Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** June 24, 1998

**TO:** Gene Mason, Pharm.D., Director, Regulatory Affairs

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Sam Maldonado, M.D., M.P.H., Acting Team Leader

**IND:**            Serial No. 020

**SUBJECT:** Comments for Protocol GS-96-412

Reference is made to your protocol amendment for study GS-96-412,            serial 020, entitled *A Phase 2, Sequential Cohort, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Trial to Assess the Safety, Tolerability, and Antiviral Activity of 4 Dose levels of Oral Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection in Subjects with Elevated Hepatic Transaminases*, dated 3 October 1997 regarding the definition changes of grade 3 and grade 4 hepatic transaminase elevations.

We concur that starting and stopping antiviral therapy may not be optimal in the treatment of chronic hepatitis B infection due to the potential risk of inducing resistant mutants. However, in light of the observed hepatotoxicity of adefovir, the amended criteria for grade 4 ALT and AST toxicities (i.e., >20X UNL and >2X baseline values) as recommended by your Adefovir DSMB are excessively high. We recommend that the criteria for grade 4 AST and ALT toxicities be reduced to >10X upper normal limit and >2X baseline levels to ensure safety for participants in adefovir studies.

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Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**DATE:** November 19, 1997

**TO:** Nanette Onizuka-Handa

**ADDRESS:** Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Jeff Murray, M.D., M.P.H., Acting Team Leader

**IND:** — Serial No. 025

**SUBJECT:** Concurrence to Restart Study Treatment for Patient 341-0041. —

As outlined in serial submission 020 dated October 3, 1997, an amendment to the protocol for study GS-96-412, entitled *A Phase II, Sequential Cohort, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Trial To Assess the Safety, Tolerability and Antiviral Activity of Four Dose Levels of Oral Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection in Subjects with Elevated Hepatic Transaminases*.

FDA/DAVDP concurs with restarting study treatment for Patient 341-0041, — with adefovir dipivoxil 60 mg or matching placebo tablets once daily.

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/s/

Debra A. Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**DATE:** November 17, 1997

**TO:** Nanette Onizuka-Handa

**ADDRESS:** Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

**FROM:** Tan Nguyen, M.D., Ph.D., Medical Officer

**THROUGH:** Jeff Murray, M.D., M.P.H., Acting Team Leader

**IND:**            Serial No. 024

**SUBJECT:** Concurrence to Restart Study Treatment for Patient 336-0015

As outlined in serial submission 020 dated October 3, 1997, an amendment to the protocol for study GS-96-412, entitled *A Phase II, Sequential Cohort, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Trial To Assess the Safety, Tolerability and Antiviral Activity of Four Dose Levels of Oral Adefovir Dipivoxil for the Treatment of Chronic Hepatitis B Infection in Subjects with Elevated Hepatic Transaminases.*

FDA/DAVDP concurs with restarting study treatment for Patient 336-0015 with adefovir dipivoxil 30 mg or matching placebo tablets once daily.

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Debra Gump, R.Ph.  
Regulatory Management Officer  
Division of Antiviral Drug Products



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-299

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: June 20, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Katherine A. Laessig, MD, Medical Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-299) for a protocol exception for — a patient of — to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.





## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-297

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: May 20, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Katherine A. Laessig, MD, Medical Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-297) for a protocol exception for — a patient of — to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

**Division of Antiviral Drug Products**  
**Food and Drug Administration**  
**Rockville MD 20857**

## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**IND:**            **SN-280**

**Drug:** **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

**Date:** **March 6, 2002**

**To:** **Martine Kraus, PhD, Associate Director, Regulatory Affairs**

**Sponsor:** **Gilead Sciences, Inc**

**From:** **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

**Through:** **Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader**

**Subject:** **APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION**

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

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## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: SN-268

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: January 25, 2002

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-268) for a protocol exception for — a patient of \_\_\_\_\_ to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

# MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND:                      SN-257

**Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

**Date:** December 5, 2001

**To: Martine Kraus, PhD, Associate Director, Regulatory Affairs**

**Sponsor: Gilead Sciences, Inc**

**From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

**Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader**

**Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION**

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-257) for a protocol exception for \_\_\_\_\_ a patient of \_\_\_\_\_ to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

**We are providing the above information via telephone facsimile for your convenience. THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me if you have any questions regarding the contents of this transmission.**



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** SN-252

**Drug:** Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

**Date:** November 15, 2001

**To:** Martine Kraus, PhD, Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

**Through:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-252) for a protocol exception for \_\_\_\_\_ a patient of \_\_\_\_\_ to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: SN-247

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: October 31, 2001

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-247) for a protocol exception for \_\_\_\_\_ a patient of \_\_\_\_\_ to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-242

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: October 31, 2001

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-242) for a protocol exception for — a patient of — to enroll in study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — /SN-218

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: June 27, 2001

To: Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-218) for a protocol exception for — a patient of — into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.





## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: \_\_\_\_\_ SN-216

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: June 27, 2001

To: Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-216) for a protocol exception for \_\_\_\_\_ a patient of \_\_\_\_\_ into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-201

Drug: **Adefovir Dipivoxil for the Treatment of Hepatitis B Virus**

Date: **June 1, 2001**

To: **Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs**

Sponsor: **Gilead Sciences, Inc**

From: **Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530**

Through: **Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader**

Subject: **REQUEST FOR INFORMATION ABOUT PROTOCOL GS-99-435**

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Reference is also made to SN-060 dated March 24, 1999 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients.*" Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

Because of the large number of protocol exceptions you have requested and we have granted, please consider amending this study to exclude the requirement that individuals must be liver transplant candidates. This would expedite enrollment of otherwise-qualified patients into the protocol and would reduce the paper work load of all parties.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: SN-204

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: May 16, 2001

To: Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTIONS

Please refer to your SN-204 for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-204) for protocol exceptions for both patients of SN-204 into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**IND:** SN-201

**Drug:** Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

**Date:** May 16, 2001

**To:** Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

**Through:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-201) for a protocol exception for a patient of \_\_\_\_\_ into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-193

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: May 4, 2001

To: Martine Kraus, PhD, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Regulatory Review Officer  
Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: APPROVAL OF REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-211 dated June 14, 2001 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-211) for a protocol exception for a patient — of — into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND:                      SN-178

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: March 5, 2001

To: Ellen F. Wallace, PhD, Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your                      for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1.*"

We have reviewed your request (SN-178) for a protocol exception for                                           into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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Please feel free to contact me if you have any questions regarding the contents of this transmission.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** SN-172

**Drug:** Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

**Date:** February 15, 2001

**To:** Ellen F. Wallace, PhD, Associate Director, Regulatory Affairs

**Sponsor:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

**Through:** Kimberly A. Struble, Pharm D, Regulatory Review Officer

**Concur:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Approval of Protocol Exception

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Please refer to your [redacted] for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-142 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1, dated August 11, 2000"*.

We have reviewed your request (SN-172) for a protocol exception for Patient ' [redacted] ' to study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

IND: — /SN-165

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: January 5, 2001

To: Ellen F. Wallace, PhD, Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-165) for a protocol exception for — patient — into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.





## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: — SN-152

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: November 10, 2000

To: Ellen F. Wallace, PhD, Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your — for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-141 dated September 7, 2000 containing protocol GS-98-435 entitled *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients, Amendment 1."*

We have reviewed your request (SN-152) for a protocol exception for — patient — into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: SN-149

Drug: Adefovir Dipivoxil for the Treatment of Hepatitis B Virus

Date: November 2, 2000

To: Ellen F. Wallace, PhD, Manager, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

Subject: REQUEST FOR PROTOCOL EXCEPTION

Please refer to your \_\_\_\_\_ for Adefovir Dipivoxil for the treatment of hepatitis B virus infection submitted December 19, 1996. Also, please refer to SN-060 dated March 24, 1998 containing protocol GS-98-435 entitled "*An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patient.*"

We have reviewed your request (SN-149) for a protocol exception for \_\_\_\_\_ patient \_\_\_\_\_ into study GS-98-435. Based on the information provided, we have concluded that your request is acceptable.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.



Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** SN-139

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** August 29, 2000

**To:** Ellen F. Wallace, PhD, Manager, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager HFD-530

**Through:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Approval for Protocol Exception for Study GS-98-435

**Comments:**

We have reviewed your request (SN-139) for a protocol exception to study GS-98-435 for \_\_\_\_\_ patient. The study site is the \_\_\_\_\_.  
Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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Please feel free to contact me if you have any questions regarding the contents of this transmission.



Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** SN-130

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** July 13, 2000

**To:** Ellen F. Wallace, PhD, Manager, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager HFD-530

**Through:** Tan T. Nguyen, MD, PhD, Medical Officer  
Katherine A. Laessig, MD, Medical Officer Team Leader (Acting)

**Subject:** Approval for Protocol Exception for Study GS-98-435

**Comments:**

We have reviewed your request (SN-130) for a protocol exception for Patient to study GS-98-435. Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:**                           /SN-129

**Drug:**                **Adefovir Dipivoxil for Hepatitis B**

**Date:**                **July 13, 2000**

**To:**                    **Ellen F. Wallace, PhD, Manager, Regulatory Affairs**

**Address:**            **Gilead Sciences, Inc**

**From:**                **Marsha S. Holloman, BS Pharm, JD, Regulatory Project  
Manager HFD-530**

**Through:**            **Jeffrey S. Murray, MD, MPH Medical Officer Team Leader**

**Subject:**            **Approval for Two Protocol Exceptions for Study GS-98-435**

**Comments:**

We have reviewed your request (SN-129) for protocol exceptions for Australian patient        and for        Italian patient to study GS-98-435. Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
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Please feel free to contact me if you have any questions regarding the contents of this transmission.



Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** SN-118

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** May 1, 2000

**To:** Bridget P. Binko, PhD, Director, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager HFD-530

**Through:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Approval for Protocol Exception for Study GS-98-435

**Comments:**

We have reviewed your request for a protocol exception for Patient 2257 into study GS-98-435 (SN/060, March 24, 1998). Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** —/SN-115

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** April 18, 2000

**To:** Bridget P. Binko, PhD, Director, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager HFD-530

**Through:** Jeffrey S. Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Approval for Protocol Exception for Study GS-98-435

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**Comments:**

We have reviewed your request for a protocol exception for Patient 2038 — into study GS-98-435 (SN/060, March 24, 1998). Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.



Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**IND:** — SN-109

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** March 14, 2000

**To:** Bridget P. Binko, PhD, Director, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager,  
HFD-530

**Through:** Kimberly Struble, Pharm D, Regulatory Review Officer

**Concur:** Jeffrey Murray, MD, MPH, Medical Officer Team Leader

**Subject:** PROTOCOL EXCEPTION FOR STUDY GS-98-435 FOR A PATIENT OF —

---

We have reviewed your request for a protocol exception for a patient of —, | — into study GS-98-435 (SN/060, March 24, 1999,) *"An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients."*

Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.





Division of Antiviral Drug Products  
Food and Drug Administration  
Rockville MD 20857

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**IND:** —

**Drug:** Adefovir Dipivoxil for Hepatitis B

**Date:** August 17, 1999

**To:** Ellen F. Wallace, PhD, Manager, Regulatory Affairs

**Address:** Gilead Sciences, Inc

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager,  
HFD-530

**Through:** Kimberly Struble, Pharm D, Regulatory Review Officer

**Concur:** Jeffrey Murray, MD, MPH, Medical Officer Team Leader

**Subject:** Protocol Exception for Study GS-98-435  
Patient —

---

**Comments:**

We have reviewed your request for a protocol exception for — into study GS-98-435 (SN/060, March 24, 1999,) *An Open Label Study of the Safety and Efficacy of Adefovir Dipivoxil for the Treatment of Liver Disease due to Lamivudine Resistant Hepatitis B (HBV) in Liver Transplant Patients.*

Based on the information provided we have concluded that this request is acceptable.

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** September 12, 2002

**TO:** Debra Birnkrant, M.D., Director  
Division of Antiviral Drug Products  
HFD-530

**VIA:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Drug Products  
HFD-530

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Regulatory Health Project Manager  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCS Review of Patient Labeling for Hepsera™ (adefovir  
dipivoxil) Tablets, NDA 21-449

The patient labeling which follows represents the revised risk communication materials for Hepsera™ (adefovir dipivoxil) Tablets. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds and have been reviewed by our office and by DDMAC. Comments are bolded, italicized, and underlined.

2 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Jeanine Best  
9/12/02 11:35:37 AM  
CSO

Anne Trontell  
9/12/02 03:11:45 PM  
MEDICAL OFFICER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** September 18, 2002

**TO:** Debra Birnkrant, M.D., Director  
Division of Antiviral Drug Products  
HFD-530

**VIA:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Drug Products  
HFD-530

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Regulatory Health Project Manager  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

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1) clarification of the seriousness of hepatitis symptoms that can occur upon drug discontinuation and, 2) to include information in the Patient Labeling to reflect the addition of information on the pregnancy registry in the Product Information (PI). We also recommend that the section, "What is the most important information I should know about HEPSERA?" remain in the patient labeling as it addresses serious, life-threatening information that appears in the PI as a Black Box Warning and provides the patient with important risk information.

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/s/

-----  
Jeanine Best  
9/18/02 04:11:03 PM  
CSO

Toni, Please sign for Anne.

Toni Piazza Hepp  
9/18/02 04:42:06 PM  
PHARMACIST

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** September 12, 2002

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HFD-530

**VIA:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Drug Products  
HFD-530

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Regulatory Health Project Manager  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

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from this portion of  
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/s/

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Jeanine Best  
9/12/02 11:35:37 AM  
CSO

Anne Trontell  
9/12/02 03:11:45 PM  
MEDICAL OFFICER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** September 18, 2002

**TO:** Debra Birnkrant, M.D., Director  
Division of Antiviral Drug Products  
HFD-530

**VIA:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Drug Products  
HFD-530

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Regulatory Health Project Manager  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Anne Trontell, M.D., M.P.H., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCS Review of Patient Labeling for Hepsera™ (adefovir  
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1) clarification of the seriousness of hepatitis symptoms that can occur upon drug discontinuation and, 2) to include information in the Patient Labeling to reflect the addition of information on the pregnancy registry in the Product Information (PI). We also recommend that the section, "What is the most important information I should know about HEPSERA?" remain in the patient labeling as it addresses serious, life-threatening information that appears in the PI as a Black Box Warning and provides the patient with important risk information.

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the review.

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/s/

-----  
Jeanine Best  
9/18/02 04:11:03 PM  
CSO

Toni, Please sign for Anne.

Toni Piazza Hepp  
9/18/02 04:42:06 PM  
PHARMACIST

**From:** Holloman, Marsha S  
**Sent:** Friday, June 28, 2002 10:34 AM  
**To:** Williams, Rebecca  
**Subject:** RE: NDA 21449  
Becky:

Attached is new labeling and PPI based on Gilead's safety update. The tradename \_\_\_\_\_ was rejected and DMETS is reviewing tradenames \_\_\_\_\_ and HEPSERA. This is a priority review with a PDUFA date of September 21, 2002. We would like to have your review by the Advisory Committee Meeting August 6. Please let me know if you need me to make a formal consult request. Also, let me know if you need further info from DAVDP.

Thanks....Marsha



Artwork in word file.doc



carton NDA submission-forvade-...



Label NDA submission-forvade-1...



carton NDA submission-hepsera-...



Label NDA submission-hepsera-1...

-----Original Message-----

**From:** Williams, Rebecca  
**Sent:** Friday, June 28, 2002 8:37 AM  
**To:** Holloman, Marsha S  
**Cc:** Rumble, Warren F  
**Subject:** NDA 21449

Hi Marsha -

I am one of the reviewers for the non-HIV/antiviral drug products. Laura Pincock recently forwarded me the draft labeling for NDA 21449 \_\_\_\_\_ (adefovir DP) for the treatment of HBV infection. Could you please let me know by what date you need to receive DDMAC comments?

Thanks,  
Becky

Rebecca Williams, Pharm.D.

**From:** Holloman, Marsha S  
**Sent:** Friday, June 28, 2002 10:36 AM  
**To:** Williams, Rebecca  
**Subject:** RE: NDA 21449  
**Becky:**

Here are the remaining files for review.

Thanks....Marsha

Marsha S. Holloman, BS Pharm, JD  
Regulatory Health Project Manager  
Division of Antiviral Drug Products  
(HFD-530) ODEIV/CDER/FDA  
phone: 301-827-2418  
fax: 301-827-2471  
email: hollomanm@cderr.fda.gov

  
6.12.02 Non Annotated Package ...

  
6.12.02 Non Annotated Package ...

  
Patient Information 03.19.02 F...

  
Patient Information 03.19.02 F...

-----Original Message-----

**From:** Williams, Rebecca  
**Sent:** Friday, June 28, 2002 8:37 AM  
**To:** Holloman, Marsha S  
**Cc:** Rumble, Warren F  
**Subject:** NDA 21449

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Thanks,  
Becky

*Adefovir Dipivoxil Tablets*  
*Gilead Sciences, Inc.*

*New Drug Application 21-449*  
*Section 18 – User Fee Cover Sheet*

---

**User Fee Cover Sheet**

In accordance with The Prescription Drug User Fee Act, Gilead Sciences, Inc. has submitted a ~~full~~ application fee for Fiscal Year 2002. A copy of the submission (dated 11 February 2002) to User Fee Identification Number 4272 is provided in this section.

**CONFIDENTIAL INFORMATION**

**GILEAD**  
S C I E N C E S

11 February 2002

Food and Drug Administration (360909)  
Mellon Client Service Center  
Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

**Subject: User Fee ID Number 4272 – NDA 21-449**

Please refer to User Fee I.D. No. 4272 and NDA 21-449 for adefovir dipivoxil for the treatment of chronic hepatitis B virus infection. Gilead Sciences plans to submit the New Drug Application for Agency review in March 2002. Enclosed please find Form FDA 3397 and payment of the User Fee in the amount of \$313,320.00.

If you have any questions or need further information, please contact me at 650-522-5722 or via facsimile at 650-522-5489. You may also contact Alan Taylor, Ph.D., Vice President, Regulatory Affairs, at 650-522-5754. We share the same facsimile number.

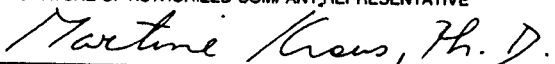
Sincerely,



Martine Kraus, Ph.D.  
Associate Director, Regulatory Affairs

Enclosures: Form FDA 3397  
Check in the amount of \$313,320.00



<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> PUBLIC HEALTH SERVICE <b>FOOD AND DRUG ADMINISTRATION</b>		Form Approved: OMB No. 0910-0297 Expiration Date: February 29, 2004.	
<b>USER FEE COVER SHEET</b>			
<i>See Instructions on Reverse Side Before Completing This Form</i>			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdufa/default.htm">http://www.fda.gov/cder/pdufa/default.htm</a>			
1. APPLICANT'S NAME AND ADDRESS Gilead Sciences, Inc.  333 Lakeside Drive  Foster City, CA 94404		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-449	
2. TELEPHONE NUMBER (Include Area Code) ( 650 ) 522-5722		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).	
3. PRODUCT NAME Adefovir Dipivoxil Tablets		6. USER FEE I.D. NUMBER 4272	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)         </div> <div style="width: 50%;"> <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)         </div> <div style="width: 50%;"> <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)         </div> <div style="width: 50%;"> <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)         </div> <div style="width: 100%; text-align: center;"> <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)         </div> </div>			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <div style="text-align: right;"> <input type="checkbox"/> YES    <input checked="" type="checkbox"/> NO         </div> (See item 8, reverse side if answered YES)			
<p>Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div>           Department of Health and Human Services            Food and Drug Administration            CBER, HFM-99            1401 Rockville Pike            Rockville, MD 20852-1448         </div> <div style="text-align: center;">           and            Food and Drug Administration            CDER, HFD-94            12420 Parklawn Drive, Room 3046            Rockville, MD 20852         </div> <div>           An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.         </div> </div>			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE Associate Director, Regulatory Affairs	
DATE February 11, 2002		DATE	

# MESSAGE CONFIRMATION

09/18/02 19:11

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
09/18	02'11"	650 522 5489	CALLING	08	OK 0000

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>	
TO (Division/Office): <b>Associate Director, Medication Error Prevention          e of Post Marketing Drug Risk Assessment, HFD-400          (Room 15B-03, PKLN Bldg.)</b>		FROM: <b>Marsha S. Holloman, BS Pharm, JD          Regulatory Health Project Manager          Division of Antiviral Drug Products, HFD-530          9201 Corporate Blvd, N432          Rockville, MD 20850</b>	
DATE 25-Jun-2002	IND. NO. ---	NDA NO. 21-449	TYPE OF DOCUMENT Trade Name Consult
NAME OF DRUG Adefovir Dipivoxil for Hepatitis B		PRIORITY CONSIDERATION Yes	DATE OF DOCUMENT 14-Jun-2002; 16-jun-2002
NAME OF FIRM: Gilead Sciences, Inc		CLASSIFICATION OF DRUG Antiviral/Systemic/Hepatitis	
DESIRED COMPLETION DATE 25-Aug-2002			
REASON FOR REQUEST			
I. GENERAL			
NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY		PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	
		RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review	
II. BIOMETRICS			
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH	
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):		CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS			
DISSOLUTION BIOAVAILABILITY STUDIES PHASE IV STUDIES		DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE			
PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS (List below) COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS			
CLINICAL		PRECLINICAL	
COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:  PDUFA DATE: 21-Sep-2002 ATTACHMENTS: Draft Package Insert, Container and Carton Labels for both FORVADE and HEPSERA CC: Archival NDA 21-449 HFD-530/Division File HFD-530/RHPM/Holloman HFD-530/CPMS/DeCicco			
HFD-530/MO/T. Nguyen HFD-530/MOTL(Actg)/Laessig HFD-530/Review Team			
SIGNATURE OF REQUESTER // Marsha S. Holloman		METHOD OF DELIVERY (Check one) MAIL <span style="float: right;">XX HAND</span>	
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER	

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** 6/26/02

**DUE DATE:** 9/6/02

**ODS CONSULT #:** 02-0138

**TO:**

Debra B. Birnkrant M.D.  
Director, Division of Anti-Viral Drug Products  
HFD-530

**THROUGH:**

Marsha Holloman  
Project Manager  
HFD-530

**PRODUCT NAME:**

**Hepsera** (Adefovir Dipivoxil Tablets) 10 mg

**NDA #:** 21-449

**NDA SPONSOR:** Gilead Sciences, Inc.

**SAFETY EVALUATOR:** Alina R. Mahmud, RPh.

**SUMMARY:** In response to a consult from the Division of Anti-Viral Drug Products (HFD-530), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Hepsera" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:**

DMETS has no objections to the use of the proprietary name "Hepsera".

This name along with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

/s/

\_\_\_\_\_  
Carol Holquist, R.Ph.  
Deputy Director,  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-5161

/s/

\_\_\_\_\_  
Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Rm. 15B32  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** August 6, 2002

**NDA NUMBER:** 21-449

**NAME OF DRUG:** Hepsera (Adefovir Dipivoxil Tablets) 10 mg

**NDA HOLDER:** Gilead Sciences, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530) for assessment of the tradename "Hepsera", regarding potential name confusion with other proprietary and/or established drug names. The sponsor submitted a Brand Institute study in support of the proposed name Hepsera. Container labels, carton and insert labeling were also submitted for review and comment.

On March 22, 2002, DMETS reviewed the name, \_\_\_\_\_ and did not recommend the use of the name (ODS consult 02-0046). In response to Agency's concerns with the use of the name \_\_\_\_\_ Gilead submitted the two alternatives: Hepsera (first choice) and \_\_\_\_\_ (second choice). Subsequent to contracting Brand Institute to evaluate the proposed proprietary names for potential risk of medication errors, the sponsor withdrew the name \_\_\_\_\_ on August 2, 2002, based on Hepsera's favorable safety profile.

**PRODUCT INFORMATION**

Hepsera is the proposed proprietary name for adefovir dipivoxil tablets. Hepsera is indicated for the treatment of chronic hepatitis B viral replication. Hepsera will be available as a 10 mg tablet and dosed once daily without regard to food.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound alike or

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> The Established Evaluation System [EES], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

look alike to "Hepsera" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the data provided by Thomson & Thomson's

Online Service<sup>4</sup> was also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies of each proposed proprietary name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

#### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Hepsera". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Hepsera. These products are listed in Table 1 (see below and page 4) along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC did not have concerns about the name Hepsera with regard to promotional claims.

Table 1

Herceptin	Trastuzumab Powder for Injection 440 mg (Rx)	The initial loading dose is 4 mg/kg infused over 90 minutes. The weekly maintenance dose is 2 mg/kg and can be infused over 30 minutes.	**S/A
Septtra	Trimethoprim and Sulfamethoxazole Tablets 80 mg/400 mg (Rx)	Dosage is individualized based on weight	**S/A
Advera	Enteral nutritional therapy (otc)	Dietary management in HIV infection or AIDS	**S/A
Heparin	Heparin Sodium Injection 10 units/mL, 100 units/mL, 200 units/mL, 400 units/mL, 1000 units/mL, 2500 units/mL, 5000 units/mL, 7500 units/mL, 10000 units/mL, 20000 units/mL, 5000 units/0.5 mL, 200 units/100 mL, 500 units/100 mL, 4000 units/100 mL, 5000 units/100 mL, 10000 units/100 mL (Rx)	Varies according to indication and usage	**L/A



<sup>4</sup> WWW location <http://www.thomson-thomson.com>.

Serax	Oxazepam Capsules: 10 mg, 15 mg, 30 mg Tablets: 15 mg (Rx)	Individualized dosage	**S/A
Keppra	Levetiracetam Tablets 250 mg, 500 mg, 750 mg (Rx)	individualized according to patients renal status	**L/A
*Frequently used, not all-inclusive. **SA (sound-alike); LA (look-alike)			

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

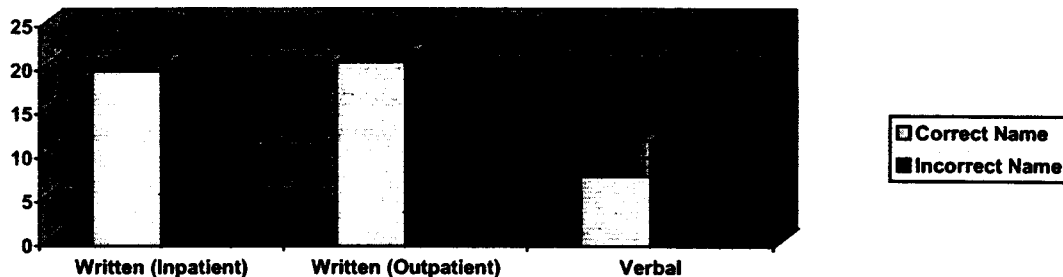
Three studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Hepsera with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the name. These studies employed 107 health care professionals comprised of pharmacists, physicians, and nurses. This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for Hepsera (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a random sample of the participating health care professionals via telephone voicemail. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Outpatient Rx:  	Hepsera Take one tablet daily
Inpatient Rx: 	

## 2. Results:

Results of the exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	26 (67%)	20 (77%)	6 (23%)
Written Outpatient	36	25 (69%)	21 (84%)	4 (16%)
Verbal Outpatient	32	20 (63%)	8 (40%)	12 (60%)
Total	107	71 (66%)	49 (69%)	22 (31%)



Among the written inpatient prescription, 6 of 26 (23%) respondents incorrectly interpreted "Hepsera". Incorrect interpretations included *Hepseva* (3), *Hepsara*, *Hepoera*, and *Hepera*.

Among the written outpatient prescriptions, 4 of 25 (16%) respondents interpreted "Hepsera" Incorrectly. Incorrect interpretations included *Epsera*, *Hepsia*, *Hepseva*, and *Hepseia*.

Among the verbal outpatient prescriptions, 12 of 20 (60%) respondents interpreted "Hepsera" incorrectly. Interpretations included *Hep-cera*, *Hetcera*, *Hepsara* (4), *Cepsara*, *Hypsera*, *Hipsera*, *Hepcera* (2), and *Sepsera*.

## C. SAFETY EVALUATOR RISK ASSESSMENT

### 1. Look-alike and sound-alike names

In reviewing the proprietary name "Hepsera", the product considered having the greatest potential for confusion include Herceptin.

*Herceptin* is the proprietary name for trastuzumab and is indicated of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who has received one or more chemotherapy regimens for their metastatic disease. Herceptin is supplied as a lyophilized sterile powder nominally containing 440 mg trastuzumab and is reconstituted with 20 mL of Bacteriostatic Water for Injection. Herceptin and Hepsera may sound similar as the names share the same number of syllables (3) and several identical letters (H, e, r, p, e). However, Herceptin and Hepsera differ in dosage form, strength, route of administration, indication, and patient population. Given the abovementioned differences and a lack of convincing sound-alike potential, the risk of confusion between Herceptin and Hepsera is minimal.



## 2. Brand Institute Study

The Brand Institute (BI) conducted a study to evaluate the potential for error between Hepsera and currently marketed brand/generic drug products.

### Section A – Practitioner Nomenclature Review: Physicians

BI asked physicians to identify any currently marketed brand or established name products that potentially sound-alike or look-alike Hepsera. They also determined if Hepsera had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to “hyperbole or false claims.” Finally, each physician provided an oral and handwritten interpretation of the Hepsera prescription. Eighty-two percent of the participants had “no issues” with the name Hepsera while the remaining 18 percent felt that the name is exaggerative or inappropriate.

BI’s analysis identified Capsaicin, Heparin, Herceptin, herplex, and Hesperidin as sound-alike and Capsaicin, Heparin, and Herceptin as look-alike names to Hepsera. The medical terms identified as being similar to Hepsera include: Hepatitis Serum and Herpes.

### Section B – Handwritten and Verbal Analysis: Pharmacists

The objective of this phase was to determine if sample Hepsera prescriptions would be interpreted as a currently marketed brand or established name products. BI states that the verbal and written prescriptions, for Hepsera, provided by the physicians in Section A were evaluated by 100 pharmacists (50 retail and 50 hospital). All respondents correctly interpreted the proposed drug name as Hepsera.

### Section C – Computer-Assisted Analysis

BI conducted a “comprehensive search of medical references” to identify brand and established name products that may sound-alike or look-alike the proposed name Hepsera. Twenty-eight names were identified. BI analyzed the names using their “Brand Reference Comparative Analysis” database and using a “Phonological and Orthographical Similarity Analysis.” The “Phonological and Orthographical Similarity Analysis” identifies a threshold of similarity between Hepsera and the twenty eight products identified during the search of the medical references. The objective of this analysis was to identify the ‘similarity between the proposed proprietary name and any sound-alike or look-alike product.’ Additionally, BI searched “Full Name Screening for Similar Medical Terms and Devices” and “Name Prefix/Suffix Screening for Similar Medical Terms, Acronyms or Abbreviations.” These two searches revealed nine medical terms/devices, prefixes, or suffixes that may be similar to Hepsera.

### Section D - Pharmacists’ Analysis – Nomenclature Advisory Board Review

‘Five actively practicing retail and hospital pharmacists’ evaluated all of the data obtained during this study and determined that based on their experience the risk of

name confusion between Hepsera and the products identified in the Brand Institute study. Thus, the review board's review was favorable for Hepsera.

#### DMETS Analysis of the Brand Institute Study

DMETS agrees with BI's analysis that none of the identified medical terms or devices, acronyms, or abbreviations are likely to interfere with the Hepsera prescribing process.

Both DMETS and BI identified four products as having either look-alike or sound-alike (Herceptin, Heparin, Advera, and Serax) properties similar to Hepsera. DMETS agrees with BI's analysis that the product profiles of these four products do not overlap and thus the potential for name confusion is minimal. BI also identified twenty-four additional products as potential look-alike or sound-alike names that were not identified during the DMETS review. Overall, DMETS agrees with BI's analysis of the low potential for name confusion with these twenty-four products.

### **III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:**

DMETS has reviewed the proposed container label, carton labeling and package insert labeling focusing on safety issues to prevent possible medication errors. One area of possible improvement has been identified in the interest of minimizing potential user error and patient safety.

Post-marketing experience has shown errors occurring with the placement of the expression of strength in close proximity with the statement of quantity. Relocate the statement of quantity to appear away from the expression of strength.

### **IV. RECOMMENDATIONS:**

A. DMETS has no objection to the use of the proprietary name "Hepsera".

B. DMETS recommends implementation of the labeling revision to minimize user error.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

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Alina R. Mahmud, RPh.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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/s/

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